A BIOAVAILABLE DOSAGE FORM OF LORATADINE

FIELD OF THE INVENTION

The present invention relates to a bioavailable oral dosage form of loratadine.

BACKGROUND OF THE INVENTION

Loratadine or ethyl 4-(8-chloro-5,6-dihydro-11H-benzo[5,6] cyclohepta [1,2-b] pyridin -11-ylidene)-1-piperidine carboxylate is useful as an antihistamine and is disclosed in U.S. Patent No. 4,282,233.

Loratadine is particularly advantageous for use of an antihistamine compared to other drugs of the same class as it is administered only once daily and has little or no sedative effects. It is therefore preferred for use by patients who have to perform mental or physical tasks requiring a high level of concentration. Loratadine however poses problems to the formulator as it has low solubility in water and therefore shows poor bioavailability characteristics.

SUMMARY OF THE INVENTION

It is an objective of the present invention to provide a bioavailable oral dosage form of loratadine, that is bioequivalent to the commercially available formulation and falls within the prescribed limits set by various International Regulatory Agencies.

Accordingly, the present invention provides a bioavailable oral dosage form of loratadine, comprising reduced particle size loratadine, such that the

average particle size ranges from about 0.1 microns to 15 microns and the average surface area falls between 1 and 2 m^2/g.

It is observed that the particle size and the surface area of loratadine is critical in achieving bioequivalence against the commercially available formulation Claritin®, marketed by Schering Corporation. The particle size of the drug is reduced thereby increasing its surface area using any of the conventional milling techniques known in the art. These include the use of ball mill, cad mill, multi mill, air jet mill etc.

In preferred embodiments of the invention, the size of the drug is reduced such that the average particle size ranges between 1 microns to 10 microns. The surface area of the milled drug is maintained between 1 and 2 m^2/g.

The milled drug is then formulated into a suitable dosage form such as tablet, capsule, syrup, suspension etc. In preferred embodiments the pharmaceutical dosage form is a tablet. The milled drug is mixed with pharmaceutically acceptable excipients such as fillers, binders and lubricants and further processed using processes conventionally known in the art such as direct compression, compaction or wet granulation.

The fillers employed in the present invention preferably comprise a pharmaceutically acceptable saccharides, including monosaccharides, a disaccharides, and polysaccharides, polyhydric alcohols, or cellulose ethers and mixtures thereof. Examples of suitable pharmaceutical fillers include sucrose, dextrose, lactose, microcrystalline cellulose, fructose, xylitol, sorbitol,

hydroxypropyl methylcellulose, mixtures thereof and the like. However, it is preferred that a soluble pharmaceutical filler such as lactose, dextrose, sucrose, or mixtures thereof be used.

The binders used in accordance with the present invention are those conventionally used in the art may be selected from the group consisting of gums such as karaya gum and locus bean gum, starch, polyvinylpyrrolidones etc. The lubricants are selected from amongst those conventionally used in the art such as magnesium stearate, zinc stearate, talc, tristearin, tripalmitin, polyethylene glycols, waxes, hydrogenated oils, aerosil and mixtures thereof.

Investigations were conducted in order to determine the effect of particle size and surface area on the bioavailability of loratadine. The blood levels of the drug were compared with that of the commercially available formulation of loratadine sold under the trade name of Claritin®. The area under the plasma concentration (loratadine) vs time curve (AUC) was determined between time "0" and time "t" to give the $AUC_{(0-t)}$ values and was then extrapolated to infinity (α) to calculate the value till there was no more drug in the plasma. This value is reported as $AUC_{(0-\alpha)}$. The maximum plasma concentration (Cmax) was also determined for each subject after each treatment.

DETAILED DESCRIPTION OF THE INVENTION

The following examples further illustrate the invention but are not intended to limit the scope of the invention.

EXAMPLE 1

Table 1.1

Ingredients	Mg/Tab
Loratadine	10.0
Lactose	86.25
Starch	1.50
Pregelatinised starch	1.50
Magnesium stearate	0.75
Total	100.0mg

The particle size of loratadine was 90% below 47.2 microns and 50% below 10.7 microns. The surface area was 1.126 m^2/g. The active and the inactive excipients are mixed and compressed to tablets. The tablets released more than 90% of the content in 0.1N HCl in USP apparatus I at 50 rpm.

The formulation was subjected to a two way cross over bioequivalence study with Claritin® (which was the reference product). Eighteen normal, male subjects were enrolled in each study. Whole blood samples were drawn at selected times following each treatment. Blood levels of the drug for both test and reference were determined and compared for the two critical parameters of AUC and Cmax (Table 1.1). Test is the formulation made according to present invention and reference is the formulation of loratadine sold under the trade name of Claritin®.

Table 1.2

	$AUC_{(0-t)}$	$AUC_{(0-\alpha)}$	C_{max} (µg/ml)
Test/ Reference (%)	81.5	85	87.7

As can be seen when the particle size of loratadine was 90% below 47 microns, the formulation was only around 80% bioavailable as compared to the commercially available formulation of loratadine sold under the trade name Claritin®.

EXAMPLE 2

The process of granulation was changed from direct compression to wet granulation to study its effect, if any, on the bioavailability of the drug.

Table 2.1

Ingredients	Mg/Tab
Loratadine	10.0
Lactose	86.50
Starch	1.50
Pregelatinised starch	1.50
Magnesium stearate	0.50
Total	100.0mg

The particle size of loratadine was 90% below 47.2 microns and 50% below 10.7 microns and the surface area was 1.126 m^2/g. The drug was mixed with the inactive excipients, and granulated using water. The granules were dried and the tablets were compressed. The tablets released 90% of the drug in 0.1 NHCl in USP apparatus 2 within 30 minutes.

This formulation was subjected to a two way cross over bioequivalence study with Claritin® on 18 normal male subjects as described in Example 1.

Table 2.2

	AUC $_{(0-t)}$	AUC $_{(0-\alpha)}$	C_{max} (μg/ml)
Test/ Reference (%)	74.8	85.1	67.5

Once again the bioavailability of the drug in our formulation was low compared to that of Claritin®, indicating that changing the processing conditions does not improve the bioavailability characteristics of the drug.

EXAMPLE 3

As loratadine of the larger particle size showed lower bioavailability as compared to the commercially available product Claritin®, it was decided to investigate the effect of reduction of particle size of the loratadine on its bioavailability.

Table 3.1

Ingredients	Mg/Tab
Loratadine	10.0
Lactose	79.75
Starch	7.5
Pregelatinised starch	2.0
Magnesium stearate	0.75
Total	100.0mg

The particle size of loratadine was 90% below 10 microns and 50% below 5 microns and the surface area was 1.54 m^2/g. The drug was mixed with the inactive excipients, granulated using water, the granules were dried, lubricated and then compressed to tablets.

The tablets released more than 90% of the drug in 0.1 NHCl in USP apparatus 2 within 30 minutes. The formulation was subjected to a two way crossover bioequivalence study on 20 healthy, male subjects as described in Example 1.

Table 3.2

	$AUC_{(0-t)}$	$AUC_{(0-\alpha)}$	C_{max} (µg/ml)
Test/ Reference (%)	100.7	91.7	95.5

As can be seen from the data, reduction in particle size of the drug led to a dramatic increase in the bioavailability of loratadine to equal that of the commercially available product Claritin®.

The next example further illustrates the importance of particle size and increased surface area on the bioavailability of loratadine.

EXAMPLE 4

Table 4.1

Ingredients	Mg/Tab
Loratadine	10.0
Lactose	80.60
Starch	7.5
Pregelatinised starch	2.0
Magnesium stearate	0.50
Total	100.0mg

The particle size of loratadine was almost similar to that used in example 3 i.e. 90% below 9 microns and 50% below 6 microns but the surface area at 2.042 m^2/g was larger than that of loratadine used in Example

3. All the active and inactives were mixed and granulated using water. The granules were dried and compressed to tablets. The tablets released 90% of the drug in 0.1 NHCl in USP apparatus 2 within 45 minutes.

The formulation was subjected to a two way crossover study on 11 normal, healthy, male subjects as described in Example 1.

Table 4.2

	$AUC_{(0-t)}$	$AUC_{(0-\alpha)}$	C_{max} (µg/ml)
Test/ Reference (%)	134	124	130

Increase in the surface area together with the reduction of particle size caused a dramatic increase in the bioavailability of the drug to almost 30% greater than that of the commercially available reference product.

These results emphasize the criticality of particle size and surface area of loratadine on its bioavailability.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.